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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/493,887	01/28/2000	Dr. Norbert Ettner	Beiersdorf 602-WCG	2789

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EXAMINER

MONSHIPOURI, MARYAM

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 10/24/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/493,887

Applicant(s)
Ettner et al.

Examiner
Maryam Monshipouri

Art Unit
1652



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4, 6-10, and 17-29 is/are pending in the application.
- 4a) Of the above, claim(s) 4, 6-10, and 17-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☒ Interview Summary (PTO-413) Paper No(s). 18
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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In response to applicant's interview with Dr. P. Achutamurthy (Art Unit 1652's supervisor) on 10/9/2003, wherein it was mutually agreed to withdraw the finality of the previous office action mailed on 5/15/2003 the following non-final office action is enclosed. It should be noted that this office action is identical to the previous office action except that the finality of said previous action is withdrawn.

A **request for continued examination** under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. **Applicant's submission filed on 10/28/2002 (Paper # 15) has been entered.**

It is noted that applicant has canceled claims 1-3, 5 and 1-16 but has not mentioned anything about the status of claims 17-20 originally presented in Paper #10 (filed 3/4/2002). Further, in currently filed amendment the new claims start with claim 17. For examination purposes it is assumed that original claim 17-20 which now depend from canceled claims are canceled. **Also, newly filed claims 17-25 are renumbered as 21-29 according to Rule 26 and from now on will be referred to as 21-29.** Applicant is required to officially cancel original claims 17-20, which depend from canceled claims in a response to this office action.

DETAILED ACTION

Claims 21-29 are under examination on the merits. Claims 4, and 6-10 are withdrawn as drawn to non-elected invention.

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Claim Objections

1. Claims 21 is objected to because of the following informalities: The terms "peptide" and "protein" are used as singular terms in the preamble and body of the claim but are referred to as plural in the closing portion of the claim. Applicant is required to refer to said terms, consistently, either in singular or in plural in the claim (and preferably in all claims). Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The examiner could not find support for the negative limitation "wherein the covalent attachment to diisocyanate-PEG matrix of the catalytically

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active peptides, proteins or portions thereof, is not mediated by catalytically inactive proteins, peptide or other inactive oligomers and polymers" recited in claim 21 (see the last portion) and its dependent claims 22-29. Hence, said limitation is considered to be **new matter**. Applicant is required to either direct the examiner to the part of the disclosure, wherein said limitation is recited or possibly delete said limitation from the claims.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 25 and 26 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "superoxide dismutase (SOD) mimic" remains unclear, as stated in previous office action (see page 4 of Paper # 9, mailed 11/06/2001). It is not clear what is said mimic and what are its properties and if it can be activated by diisocyanates.

6. Claims 23-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear whether the portions of catalytically active peptides proteins or portions of catalase (claim 23) and SOD (claim 24) should retain catalytic activity or not.

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7. ***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. Claims 21-26 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fortier (U.S. patent No. 5,733,563, 1998, cited previously) in view of Galin et al. (Cited previously), according to previous office action. Fortier teaches a PEG (polyethylene glycol) hydrogel of a molecular weight of from 2000 to 35000 to which enzymes such as catalase are crosslinked through their amino groups optionally in the presence or absence of albumin (see column 14, wherein PEG/catalase hydrogel preparation in the absence of albumin is taught), wherein the crosslinking agent is 4-nitrophenyl chloroformate.

Fortier does not teach a hydrogel or a method of preparation thereof wherein the PEG activating agent is diisocyanate and wherein said PEG reacts via its urea groups. Galin teaches the reaction of PEG (of molecular weight 2750-10600) with diisocyanates (including 1, 6-

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hexamethylene diisocyanate) which inherently involves binding of NCO to OH residues of PEG (see abstract) exposing NCO residues of Cyanate in place of OH residues of glycol.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to start with the PEG of Fortier and use diisocyanate activating agent according to Galin in order to develop new processes for PEG crosslinking to enzymes or products such as SOD or catalase or synthetic derivatives (mimics) of said enzymes (see 112 second rejection above), which for retaining catalytic activity inherently require a porphyrin comprising a manganese, copper, iron or magnesium etc., resulting in stable PEG/enzyme hydrogels.

One of ordinary skill in the art is motivated in preparing SOD-, SOD mimics- or catalase- PEG corsslinked hydrogels because Fortier explicitly teaches that PEG-catalase gels prepared by activating with 4-nitrophenyl chloroformate are unstable (see column 14 of Fortier) implying that new improved hydrogel/enzyme cross linking methods should be attempted. Such attempts obviously include changing the chemical structure of activating agent to activators such as diisocyanates of Galin.

One of ordinary skill in the art has a reasonable expectation of success in reacting anhydrous PEG of Fortier with diisocyanate of Galin and remove the solvent after PEG

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activation by washing or filtration, reacting the activated PEG with catalase or SOD in an appropriate buffer and optionally washing the final gel to obtain a purified PEG/enzyme hydrogel complex. This is because Galin has shown success in activating PEG with diisocyanate by creating CO-NH residues which according to prior art can successfully bind to NH₂ residues on all chemical structures (natural or synthetic) including proteins/enzymes or mimics thereof, rendering the claimed invention obvious.

In traversal of this rejection applicant argues the following : (1) that Galin's reference is not enabling to create a PEG hydrogel having covalently attached active enzymes. Galin would be enabling for creating copolymerized matrices comprising PEG and urethane groups. There is not teaching for the applicability to other uses. The claimed hydrogel possesses active enzymes coupled directly to the PEG, something that Fortier does not disclose. Nor does he disclose or suggest that an diisocyanate would achieve the result claimed herein. Thus, there is no motivation to combine the references because there is no reasonable expectation of success.

(2) With respect to Gould's '955 patent applicant again is of the opinion that said reference is not enabling because it does not teach activation of PEG. Gould's hydrogels do not bind anything, they merely entrap fluid. Hence, according to applicant neither Gould nor Galin

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hint that one could use isocyanates with Fortier's PEG to reach a hydrogel comprising covalently attached and active enzymes and therefore the rejection should be withdrawn.

These arguments were fully considered but were found **unpersuasive**. In response to applicant's **first** argument the examiner maintains that Galin's referencedoes not to be enabling to create PEG/enzyme(protein) hydrogels because, as mentioned previously, is merely cited to indicate that prior art teaches about PEG (specially in M.Wt range of 8000-18000 g/mol) activation with diisocyanates. Had Galin taught the covalent attachment of enzymes to its activated hydrogel, it would have been anticipatory to this invention.

Further, in contrast to applicant's view Fortier teaches direct convent attachment of its catalase to activated PEG (see column 14). Even though Fortier does not disclose, specifically, any information about diisocyanates, it certainly provides motivation in trying out new PEG/enzyme(protein) cross linking methods, because it states that gels formed by direct crosslinking of PEG with catalase using 4-nitrophenyl chloformate are unstable. As mentioned previously, new attempts for preparing more stable PEG-enzyme (protein) hydrogels involve trying out new activating agents, which inherently include diisocyanates. Thus, the examiner

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maintains that the motivation to combine the cite art in order to arrive at current invention is clearly present in the prior art.

Furthermore given the enormous amount of knowledge accumulated in the prior art with regards to activating PEG's, at the time of this invention, one of ordinary skill had a reasonable expectation of success in covalently attaching any compound including enzymes, proteins and derivatives thereof to PEG's using any of the well known activating agents including diisocyanates.

With respect to applicant's **second** argument the examiner again would like to point out that said reference, similar to Galin reference, was merely cited to indicate that the concept of PEG reaction(activation) with diisocyanates were known and successfully preformed in the prior art for various purposes. Whether said gels could react with or bind proteins after activation, is not relevant because said reference was merely cited for providing conceptual information and not as 102/103 art against this invention. The concept of direct protein/enzyme cross linking to PEG's comes from Fortier not from Gould or Galin.

Once again the examiner would like to emphasize that Fortier teaches all the limitations of this invention except for the type of activating agent used and the reaction (activation) of

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diisocyanates (activating agent of this invention) with PEG's are clearly disclosed in Galin. Thus, the examiner finds no convincing reason to withdraw the rejection.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Maryam Monshipouri, Ph.D. whose telephone number is (703) 308-1083.

The Examiner can normally be reached daily from 8:30 A.M. to 5:00 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. P. Achutamurthy, can be reached at (703) 308-3804. The OFFICIAL fax number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

M. Monshipouri
MARYAM MONSHIPOURI, PH.D.
PRIMARY EXAMINER